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REGULAR ARTICLE

Special Section on Transition Metal Catalyzed Synthesis of Medicinally Relevant Molecules

Copper-catalyzed stereo- and chemoselective synthesis of enaminones *via* Michael type addition

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Abstract. An efficient strategy for the synthesis of α,β-unsaturated enaminones by the nucleophilic addition of *N*-heterocycles such as indole and imidazoles onto electronically bias alkynones under mild reaction conditions is described. Key feature of this reaction is the chemoselective addition of *N*-heterocycles onto ynones without affecting the 1° amino groups (aromatic and aliphatic) of 5-aminoindole and tryptamine. The stereochemistry of the products was controlled by the tuning of reaction time. The mechanism of the reaction involves the Michael type addition of *N*-heterocycles on ynones *via* allene formation.

Keywords. Copper; alkynones; hydroamination; Michael addition; enaminones.

1. Introduction

For more than a century, 1,3-dicarbonyl compounds and their derivatives have been one of the most versatile and frequently employed C-3 synthons in organic synthesis.[1] Among them, enaminones[2] have been used in synthetic chemistry since a long time. One reason for their widespread application is their versatile reactivity, both as electrophiles and nucleophiles. Enaminones are the vinylogous amides that are resonance-stabilized and known to have high nucleophilicity. They are the enamines of carbonyl compound resembling chalcones and are well known for their intrinsic pharmacological and biological properties.[3] Many reports on the antioxidants, antiproliferative, antibacterial, anticancer, cytotoxic agents and chemopreventive properties of enaminones have been discussed in the literature.[4]

Enaminones occupy an important place as intermediates in target oriented organic synthesis.[5] They are considered as vital synthetic targets because of the subsequent reactivity of their double bond, often working as substrates for addition or redox reaction. Enamine and imines both function as reagents for the introduction of *N*-containing moieties into a synthetic sequence. The π-electron delocalization and presence of α,β-unsaturated bond are the two specific characteristic of enaminones which makes them reactive. Due to their significant utility in organic synthesis, a number of methods have been developed for the preparation of enaminones.[6,7] For decades, enaminones were prepared by the general reaction of amines and 1,3-diketones which are established substrates in heterocyclic chemistry.[8] However; the conventional methodology suffers from various drawbacks. The utilization of ynones is a common strategy in the synthesis of many biologically important compounds.[9]

In 2003, Muller and co-workers[5b] described Sonogashira coupling of acid chloride followed by addition of non-heterocyclic amines on to alkynone (Scheme 1a). Later, Jiang group[10] reported the multicomponent domino synthesis of tetrahydropyridine using L-proline as a catalyst (Scheme 1b). Subsequently, Chauhan and researchers[11] reported the two-step synthesis of chalcones derivatives *via* reaction of indolyl acetophenone with carbonyl substrate (Scheme 1c). In 2012, Trofimov and co-workers[12] demonstrated the superbase promoted α-vinylation of aliphatic, alicyclic, and alkyl aromatic ketones with arylacetylenes for the synthesis of β,γ-unsaturated ketones (Scheme 1d). In reference to the above approaches and ongoing research of our group on hydroamination chemistry,[13,14] herein we report copper-catalyzed nucleophilic addition of *N*-heterocycles onto

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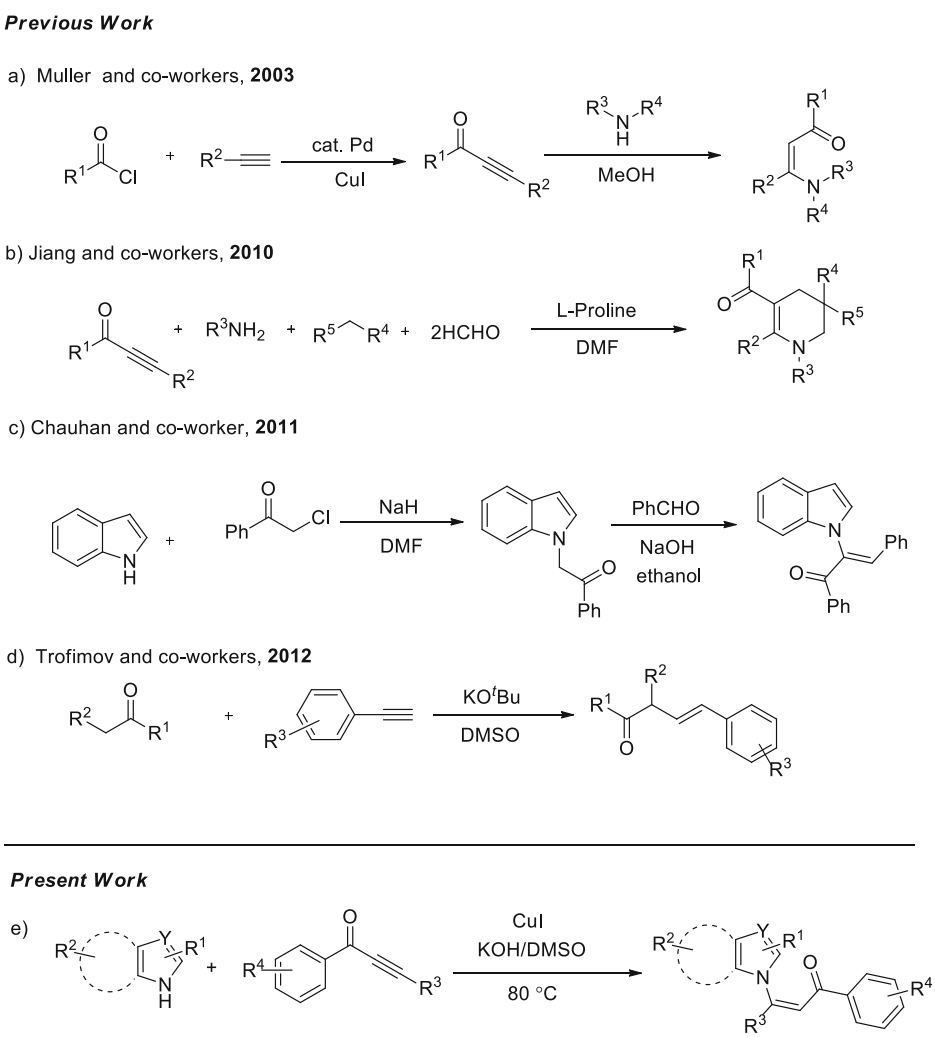


Scheme 1. Previous strategies vs. present work.

alkynones to synthesize α,β-unsaturated enaminones (Scheme 1e).

2. Experimental

2.1 *Material and physical measurements*

The chemicals and reagents used for the synthesis were obtained from commercial sources. Solvents were distilled from an appropriate drying agent. Heterocycles, benzoyl chloride and alkynes (Sigma Aldrich) were used as received. All other chemicals and solvents were of analytical grade. All the reactions were performed in an oven-dried Schlenk flask under an argon atmosphere. Column chromatography was performed using neutral and basic alumina. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over the I_2 chamber. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, br s = broad), coupling constants in Hertz, and integration. High-resolution mass spectra were recorded with q-TOF electrospray mass spectrometer, and Infrared spectra were recorded on an FT-IR spectrophotometer.

2.2 *Synthesis of alkynone* **2**

The alkynone **2** was prepared by the Sonogashira coupling reaction of corresponding benzoyl chloride with terminal alkynes. To a solution of $Pd(PPh_3)_2Cl_2$ (2 mol%) and CuI (4 mol%) in THF under an inert atmosphere, alkyne (0.5 mmol), benzoyl chloride (0.5 mmol) and base triethyl amine (0.5 mmol) were added. Resulting mixture was stirred at 25 °C (room temperature) for 30–45 min. The progress of the reaction was monitored by TLC. After the complete consumption of the starting substrate, the reaction mixture was extracted with ethylacetate (5 mL × 3) and evaporated under reduced pressure. The crude reaction mixture was purified using silica gel column chromatography (EtOAc: Hexane ::5: 95).

2.3 *Synthesis of enaminones* **3**

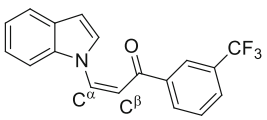
To a solution of *N*-heterocycle **1** (0.5 mmol) in DMSO and finely crushed KOH (0.2 equiv.), alkynone **2** (0.3 mmol) and CuI (2 mol%) was added. Resulting mixture was heated at 80 °C for 10–15 min. Progress of the reaction was monitored by TLC. After the complete consumption of the starting substrate, reaction mixture was brought to room temperature. The reaction mixture was extracted with ethylacetate (5 mL × 3) and evaporated under reduced pressure. The crude reaction mixture was purified using silica gel column chromatography.

2.4 *Characterization of alkynone* **2a**

1-(3-(Trifluoromethyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one. The product was obtained as a pale white oil (117.4 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.30 (d,J = 7.3 Hz, 1H), 7.84 (d,J = 9.5 Hz, 1H), 7.65–7.60 (m, 1H), 0.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 136.9, 132.6, 130.4, 129.3, 126.3 (q, J = 3.8 Hz, 1C), 102.4, 100.1, −0.8. HRMS (EI) $[M]^+$ Calcd. for $[C_{13}H_{13}F_3OSi]$ 270.0688, found 270.0688.

2.5 *Characterization of compound* **3a**

(*Z*)-3-(1*H*-Indol-1-yl)-1-(3-(trifluoromethyl)phenyl)prop-2-en-1-one



Compound **3a** was prepared by the addition of 0.2 equiv. of KOH and CuI (2 mol%) in the solution of indole **1a** and 1-(3-(trifluoromethyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one **2a** in DMSO. The reaction mixture was heated at 80 °C for 15 min. The structure of compound **3a** was established on the basis of its spectral data analysis. Its high-resolution mass spectrum showed $[M]^+$ peak at m/z 315.0871, which confirmed its molecular formula to be $C_{18}H_{12}F_3NO$. In the ^{1}H NMR spectrum in $CDCl_3$ at 400 MHz, the characteristic peaks of the styryl protons at C^α and C^β appeared at δ 8.14 and 7.74 ppm with a coupling constant J of 7.7 and 7.8 Hz, respectively, suggesting the formed isomer as a *Z*-isomer. Similarly, the ^{13}C NMR spectrum in $CDCl_3$ at 100 MHz, appearance of the quartet carbon at δ 125.1 ppm shows the formation of an addition product. The peaks of all other protons and carbons of the molecule were present in ^{1}H and ^{13}C NMR spectra of the molecule in Supplementary Information.

3. Results and Discussion

3.1 *Optimization of the reaction condition*

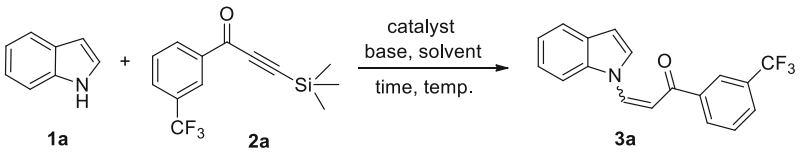
To identify the optimal reaction conditions, we have screened various bases and solvents under certain interval of time at different temperatures. We began our investigation using indole **1a** and 1-(3-(trifluoromethyl) phenyl)-3-(trimethylsilyl)prop-2-yn-1-one **2a** as our model substrates (Table 1).

Inspired by our previous conditions for hydroamination, we performed the reaction of **1a** with **2a** in the presence of 0.2 equiv. of KOH in DMSO at 120 °C for 30 min yielded 24% of the *E*-isomer **3a** (Table 1, entry 1). Decreasing the reaction temperature from 100 °C to 80 °C provided the desired product **3a** in 44% and 54% yield, respectively (entries 2 and 3). Lowering the reaction time from 30 min to 20 min leads to a mixture of *E* and *Z* stereoisomers (entry 4). On tuning the reaction time to 15 min, the *Z*-isomer **3a** was obtained in 59% yield (entry 5). Further lowering the reaction time leads to the incompletion of the reaction (entries 6 and 7). Enhancing the amount of KOH to 0.5 equiv. did not make any significant effect on the yield of the reaction (entry 8). Interestingly, the addition of 2 mol% of CuI improved the yield of hydroaminated product **3a** to 74% (entry 9). However, no significant change in the yield of the product was observed when 5 mol% of CuI was used (entry 10). Other inorganic bases such as NaOH, $CsOH{\cdot}H_2O$, and K^+O^tBu were found to be ineffective for the reaction (entries 11–13). Inferior results were obtained when Et_3N was used as a base (entry 14). Next, we screened the solvents for the designed reaction and to our interest moderate yield was obtained with NMP, though other solvents like toluene, DMF and MeCN failed to give the desired product (entries 15–18).

3.2 *Hydroamination of alkynones with N-heterocycles*

Our preliminary investigation revealed that the optimal reaction condition for the synthesis of diversely substituted styryl enaminones was 2 mol% of CuI and 0.2 equiv. KOH in DMSO at 80 °C for 15 min. Addition of *N*-heterocycles **1a–h** on alkynones **2a–f** provided the corresponding hydroaminated products **3a–u** in moderate to good yields (Table 2, entries 1–21). It was noticed that the nature of the heteroarenes and the substituents attached to the triple bond has a major impact on the success of the process. It was motivating to find that reaction of heterocycles **1a** with electron-withdrawing alkynone 1-(3-(trifluoromethyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one **2a** provided *Z*-isomer **3a** as major product with the hydrolysis of TMS within 15 min in 74% yield (entry 1). High temperature and longer reaction time led to the decomposition of product. Intermolecular addition of indole **1a** on to internal alkynone **2b–d** provided the hydroaminated products **3b–d** in 70%, 72% and 70% yields, respectively

Table 1. Optimization of the reaction conditions.[a]



Entry	Alkyne	Base (equiv.)	Solvent	Time(min)/ T °C	Yield (%)[b] **3a**(E:Z)[c]
1	**2a**	KOH (0.2)	DMSO	30/120	24 (95:05)
2	**2a**	KOH (0.2)	DMSO	30/100	44 (95:05)
3	**2a**	KOH (0.2)	DMSO	30/80	54 (95:05)
4	**2a**	KOH (0.2)	DMSO	20/80	52 (60:40)
5	**2a**	KOH (0.2)	DMSO	15/80	59 (00:100)
6	**2a**	KOH (0.2)	DMSO	10/80	45 (00:100)
7	**2a**	KOH (0.2)	DMSO	05/80	33 (00:100)
8	**2a**	KOH (0.5)	DMSO	15/80	56 (00:100)
9[d]	**2a**	**KOH (0.2)**	**DMSO**	**15/80**	**74 (00:100)**
10[e]	**2a**	KOH (0.2)	DMSO	15/80	75 (00:100)
11[d]	**2a**	NaOH (0.5)	DMSO	15/80	69 (00:100)
12[d]	**2a**	$CsOH{\cdot}H_2O$ (0.5)	DMSO	15/80	62 (00:100)
13[d]	**2a**	K^+O^tBu (0.5)	DMSO	15/80	60 (00:100)
14[d]	**2a**	Et_3N (0.5)	DMSO	15/80	NR
15[d]	**2a**	KOH (0.2)	Toluene	15/80	NR
16[d]	**2a**	KOH (0.2)	DMF	15/80	NR
17[d]	**2a**	KOH (0.2)	MeCN	15/80	Trace
18[d]	**2a**	KOH (0.2)	NMP	15/80	56 (00:100)

[a]Reactions were performed using N-heterocycle **1a** (0.5 mmol), alkyne **2a** (0.3 mmol) in 2.0 mL of solvent under nitrogen atmosphere. [b]Total yield of two isomers. [c]Sterioisomeric ratio. [d]CuI (2 mol%).[e]CuI (5 mol%).

(entries 2–4). Electron-rich amines like 3-methylindole **1b** reacted smoothly with alkynones **2b–d** and providing the desired products **3e–g** in good yields (entries 5–7). Interestingly, chemoselective hydroamination was obtained when tryptamine **1c** and 5-aminoindole **1d** were used as substrates without affecting the primary amine group (entries 8–15). The 5-methoxyindole **1e** and 5-bromoindole **1f** were compatible under our screened conditions and afforded the Z-styryl alkynones **3p–r** in 63–59% yield (entries 16–18). The NOE studies of the enaminone **3p** confirm the orientation of the rings in the product. Subtle switching from indole nucleus to imidazole moiety **1g** successfully gave the addition product **3s** in 67% yield (entry 19). Similarly, the reaction of sterically hindered heterocycle **1h** with 1-(2-bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-one **2b** and 3-(*m*-tolyl)-1-(3-(trifluoromethyl) phenyl)prop-2-yn-1-one **2f** afforded the styrylenaminones **3t** and **3u** in 61 and 60% yield respectively (entries 20 and 21). However, the alkyl ynone **2g** failed to provide the hydroaminated product **3v** instead an inseparable complex mixture was obtained (entry 22).

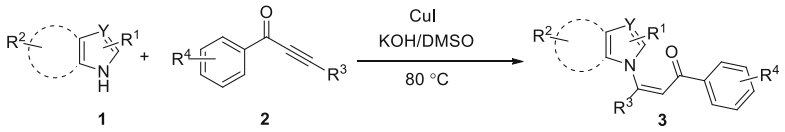
3.3 *Plausible mechanism*

The addition of N-heterocycle **1** to the corresponding alkynone **2** takes place in accordance with Michael addition reaction (Scheme 2). The hydroxide generates a nucleophile **P** that attacks the electrophilic alkyne conjugated with the carbonyl group giving rise to an allene **Q** *via* polarization of Cu. Species Q rearranges into species **R** which undergoes protometal leading to the formation of enaminone **3**.

4. Conclusions

We have developed an efficient and simple strategy for the synthesis of α,β-unsaturated enaminones by the nucleophilic addition of N-heterocycles onto alkynones under mild reaction conditions. The addition of catalytic amount of copper facilitates the attack of nucleophile onto alkynones. The developed protocol provides regio-, stereo- and chemoselective syntheses of Z-styryl enaminones. The chemoselective addition of N-heterocycles

Table 2. Synthesis of styrylenaminones by the addition of *N*-heterocycles and alkynones.[a]



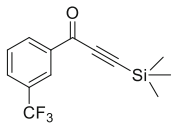
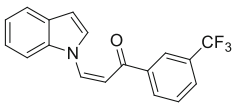
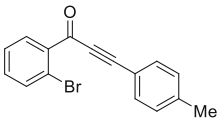
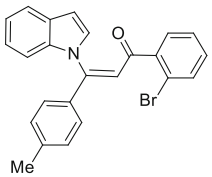
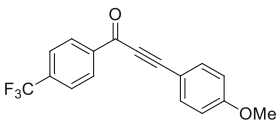
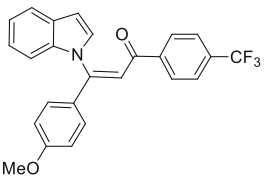
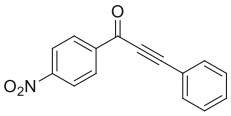
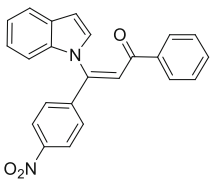
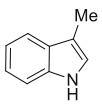
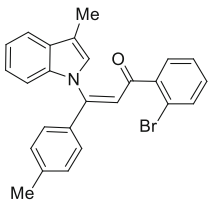
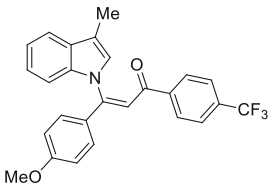
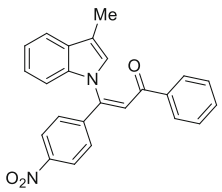
Entry	*N*-heterocycle 1	Alkynones 2	Product 3	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	74
2	**1a**	 **2b**	 **3b**	70
3	**1a**	 **2c**	 **3c**	72
4	**1a**	 **2d**	 **3d**	70
5	 **1b**	**2b**	 **3e**	71
6	**1b**	**2c**	 **3f**	69
7	**1b**	**2d**	 **3g**	71

Table 2. (*contd.*)

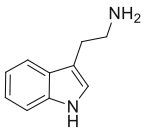
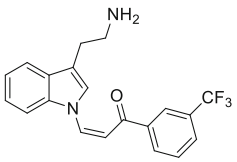
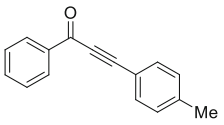
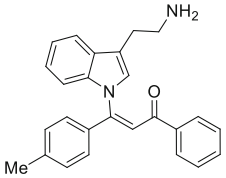
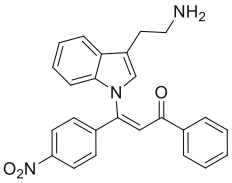
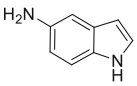
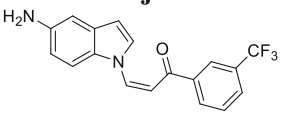
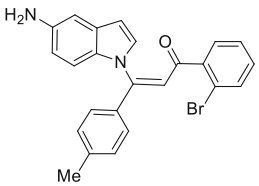
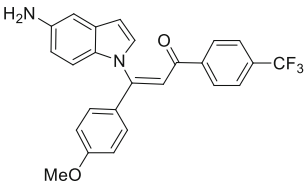
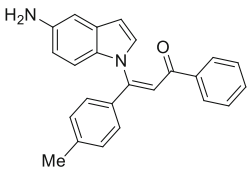
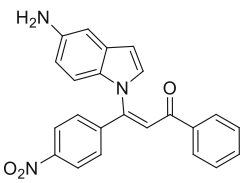
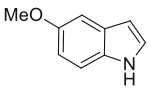
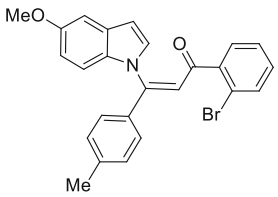
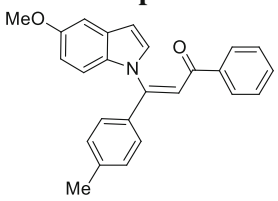
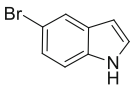
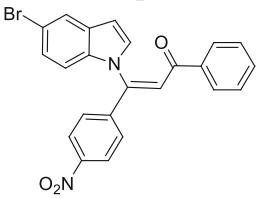
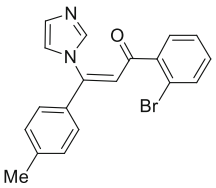
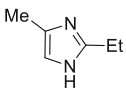
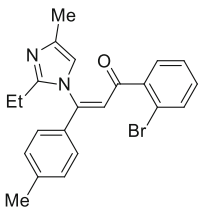
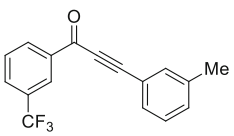
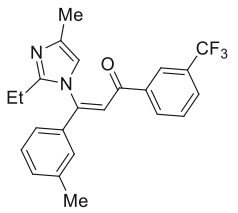
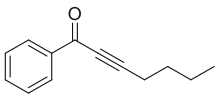
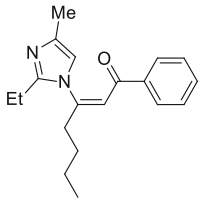
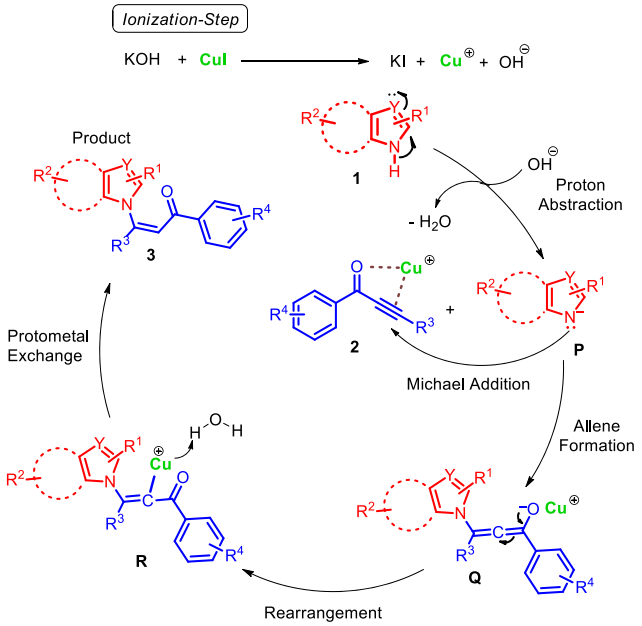
8	 **1c**	**2a**	 **3h**	65
9	**1c**	 **2e**	 **3i**	68
10	**1c**	**2d**	 **3j**	61
11	 **1d**	**2a**	 **3k**	69
12	**1d**	**2b**	 **3l**	69
13	**1d**	**2c**	 **3m**	67
14	**1d**	**2e**	 **3n**	69
15	**1d**	**2d**	 **3o**	62

Table 2. (*contd.*)

16	 **1e**	**2b**	 **3p**	60
17	**1e**	**2e**	 **3q**	63
18	 **1f**	**2d**	 **3r**	59
19	 **1g**	**2b**	 **3s**	67
20	 **1h**	**2b**	 **3t**	61
21	**1h**	 **2f**	 **3u**	60
22	**1h**	 **2g**	 **3v**	-[c]

[a]The reactions were performed using *N*-heterocycle **1** (0.5 mmol), alkyne **2** (0.3 mmol), CuI (2 mol%) and KOH (0.2 equiv.) as base in 2.0 mL of DMSO at 80 °C for 15 min under nitrogen atmosphere. [b]Yield of isolated product. [c]Inseparable complex mixture.



Scheme 2. Probable mechanism *via* Michael addition.

onto alkynones proceeds without affecting 1° amino groups (aromatic and aliphatic) present in the substrate and provides a synthetically useful handle in the products for further elaboration. The method involves a facile route, utilizing simple and easily accessible starting materials under non-toxic environment increases the synthetic utility of the developed protocol.

Supplementary Information (SI)

Characterization data and copies of ^{1}H, ^{13}C NMR and HRMS spectra for selected compounds are reported, which available free of charge at www.ias.ac.in/chemsci.

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